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Invited Perspective: A Wise Choice: Using Murine Models to Demonstrate Dental Effects following Exposure to Endocrine-Disrupting Compounds

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Developmental defects of tooth enamel are prevalent and can originate during prenatal, neonatal, and postnatal periods of tooth development (odontogenesis). Well over 100 environmental and genetic factors have been associated with developmental defects of tooth enamel.[1] Among environmental factors examined in depth are systemic exposure to fluoride (dental fluorosis) and polychlorinated biphenyls.[2,3] In a new study in Environmental Health Perspectives, Bui et al.[4] followed up on their earlier investigations of endocrine-disrupting compounds (specifically bisphenols) impacting tooth development.[5–8] Here the authors focused on developmental disturbances of enamel formation resulting from long-term exposures to di-(2-ethylhexyl) phthalate (DEHP), a plasticizer that is widely present in the environment and also has endocrine-disrupting properties.[9,10] The authors' use of mice to study the effects of endocrine disruptors during odontogenesis is a wise choice for a number of reasons, including continuous enamel formation (amelogenesis) throughout the mouse's life.

In the new study, adult C57BL/6J male and female mice were exposed to varying doses of DEHP in their food for 12 wk. DEHP was adjusted for body weight to keep exposures within the limits established for total dietary intake by the European Food Safety Authority.[11] The authors observed clinically visible incisor enamel defects, including opacities and loss of color, as well as reduced mineral densities and enamel hardness. They attributed the latter to delayed enamel mineralization caused by DEHP. This study is largely descriptive and shows dose-dependent effects, but it also identifies sexual dimorphism, with the teeth of males affected more than those of females.

Much of our understanding of odontogenesis comes from studies of mice. Odontogenesis requires epithelial–mesenchymal interactions; differentiation of precursors of odontoblasts and ameloblasts, which form the dentin and enamel, respectively; and distinct mineralization processes leading to dentin and enamel development.[12] Studies in rodents have also identified the presence of steroid hormone receptors during amelogenesis.[7,13] This is highly relevant to the work of Bui et al.[4]

A challenge in investigating how environmental toxicants, such as phthalates, disturb tooth and enamel development in humans stems from the fact that odontogenesis begins during the embryonic period and is concealed within bone. In humans, primary (deciduous) teeth begin their morphogenesis journey at ~6 wk of gestation. Mineralization of primary teeth begins at ~4 months of gestation for central incisors, lateral incisors, canines, and first and second molars. The fully formed primary teeth erupt into the oral cavity between 6 (central incisors) and 30 (molars) months of age.[14] Development of permanent teeth follow their own chronology and eruption schedule. It is only after teeth erupt into the mouth that the impact of exposures to environmental toxicants on human tooth and enamel development can be visualized.

Rodents, on the other hand, have continuously erupting incisors. In mice, the wear and growth of incisors is generally in equilibrium. In adult mice, incisors grow approximately 2 mm/wk, with a complete turnover of the incisors in approximately 5–9 wk.[15] This allows exposure studies to occur during postnatal periods in mice and to target the different stages of enamel formation within a short period of time. In addition, mice have several unique characteristics that permit mechanistic studies of tooth formation. First, both inbred mouse strains and genetically diverse lines of mice can be used to dissect genetic pathways and networks following environmental exposures. Certain inbred strains of mice respond differentially to environmental exposures (e.g., dental fluorosis following fluoride exposure[16]), whereas genetically modified mice are readily available or can be created to provide useful tools for investigating particular pathways and networks.

The work of Bui et al.[4] requires further investigations to better understand the sexual dimorphism observed. For example, the social nature of male mice may differ from that of female mice, and males' greater need to gnaw on caging might be a factor in damage to the incisors. Because DEHP can have a systemic effect, it remains possible that the phenotype present in the erupting incisors is due to altered mineral homeostasis, altered renal function, or endocrine disturbances. These possibilities require further investigation. Finally, future studies might assess whether amelogenesis returns to normal when DEHP is removed from the diet. Such studies would provide insight into whether the stem cell pool giving rise to ameloblasts may be altered due to DEHP exposure.

References

1. Collignon AM, Vergnes JN, Germa A, Azogui S, Breinig S, Hollande C, et al. 2022. Factors and mechanisms involved in acquired developmental defects of enamel: a scoping review. Front Pediatr 10:836708, PMID: 35281236, https://doi.org/10.3389/fped.2022.836708.
2. Everett ET. 2011. Fluoride's effects on the formation of teeth and bones, and the influence of genetics. J Dent Res 90(5):552–560, PMID: 20929720, https://doi.org/10.1177/0022034510384626.
3. Jan J, Vrbic V. 2000. Polychlorinated biphenyls cause developmental enamel defects in children. Caries Res 34(6):469–473, PMID: 11093020, https://doi.org/10.1159/000016625.
4. Bui AT, Houari S, Loiodice S, Bazin D, Sadoine J, Roubier N, et al. 2022. Use of dental defects caused by low-dose di(2-ethylhexyl)phthalate as an early marker of exposure to environmental toxicants. Environ Health Perspect 130(6):067003, https://doi.org/10.1289/EHP10208.
5. Jedeon K, De la Dure-Molla M, Brookes SJ, Loiodice S, Marciano C, Kirkham J, et al. 2013. Enamel defects reflect perinatal exposure to bisphenol A. Am J Pathol 183(1):108–118, PMID: 23764278, https://doi.org/10.1016/j.ajpath.2013.04.004.
6. Jedeon K, Houari S, Loiodice S, Thuy TT, Le Normand M, Berdal A, et al. 2016. Chronic exposure to bisphenol A exacerbates dental fluorosis in growing rats. J Bone Miner Res 31(11):1955–1966, PMID: 27257137, https://doi.org/10.1002/jbmr.2879.

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7. Jedeon K, Loiodice S, Salhi K, Le Normand M, Houari S, Chaloyard J, et al. 2016. Androgen receptor involvement in rat amelogenesis: an additional way for endocrine-disrupting chemicals to affect enamel synthesis. Endocrinology 157(11):4287–4296, PMID: 27684650, https://doi.org/10.1210/en.2016-1342.
8. Jedeon K, Marciano C, Loiodice S, Boudalia S, Canivenc Lavier MC, Berdal A, et al. 2014. Enamel hypomineralization due to endocrine disruptors. Connect Tissue Res 55(suppl 1):43–47, PMID: 25158179, https://doi.org/10.3109/03008207.2014.923857.
9. Griffiths WC, Camara P, Lerner KS. 1985. Bis-(2-ethylhexyl) phthalate, an ubiquitous environmental contaminant. Ann Clin Lab Sci 15(2):140–151, PMID: 3994287.
10. Koo HJ, Lee BM. 2005. Human monitoring of phthalates and risk assessment. J Toxicol Environ Health A 68(16):1379–1392, PMID: 16009652, https://doi.org/10.1080/15287390590956506.
11. EFSA Panel on Food Contact Materials, Enzymes and Processing Aids; Silano V, Barat Baviera JM, Bolognesi C, Chesson A, Cocconcelli PS, et al. 2019. Update of the risk assessment of di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and di-isodecylphthalate (DIDP) for use in food contact materials. EFSA J 17(12):e05838, PMID: 32626195, https://doi.org/10.2903/j.efsa.2019.5838.
12. Matalová E, Lungová V, Sharpe P. 2015. Development of tooth and associated structures. In: *Stem Cell Biology and Tissue Engineering in Dental Sciences*. Vishwakarma A, Sharpe P, Shi S, Ramalingam M, eds. New York, NY: Academic Press, 335–346.
13. Houari S, Loiodice S, Jedeon K, Berdal A, Babajko S. 2016. Expression of steroid receptors in ameloblasts during amelogenesis in rat incisors. Front Physiol 7:503, PMID: 27853434, https://doi.org/10.3389/fphys.2016.00503.
14. Logan WGH, Kronfeld R. 1933. Development of the human jaws and surrounding structures from birth to the age of fifteen years. J Am Dent Assoc (1922) 20(3):379–427, https://doi.org/10.14219/jada.archive.1933.0080.
15. Ness AR. 1965. Eruption rates of impeded and unimpeded mandibular incisors of the adult laboratory mouse. Arch Oral Biol 10(3):439–451, PMID: 5231526, https://doi.org/10.1016/0003-9969(65)90109-3.
16. Everett ET, McHenry MAK, Reynolds N, Eggertsson H, Sullivan J, Kantmann C, et al. 2002. Dental fluorosis: variability among different inbred mouse strains. J Dent Res 81(11):794–798, PMID: 12407097, https://doi.org/10.1177/0810794.